E. Dorbelf #138

DEPARTMENT OF HEALTH, EDUCATION, AND ~~WELFARE~~

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National Institute of Mental Health
Addiction Research Center
U.S. Public Health Service Hospital
Lexington, Kentucky

I must apologize for not writing to you sooner but, as you know, I was away for most of the summer. Since my return the possibility has arisen that we may get a new building which would provide new space for research here. I therefore have been working under multiple pressures and haven't had a great deal of free time.

Budget. To my disappointment the National Institute of Mental Health was not able to provide any additional funds to pick up any of the personnel currently in our project. I therefore continue to be dependent on you. I have asked NIMH again to include an item for salaries of part or all of these employees in the budget for fiscal 1959, but there is, of course, no way of knowing if this can be done. I will try to keep you informed.

LSD Congeners with Sedative Effects. I mentioned briefly in a letter dated 26 May 1958 the sedative effects observed with compounds of this type. Two of these (agroclavine and dihydro-agroclavine) were obtained from Takeda Laboratories in Japan. A third compound (No. 23194, Eli Lilly & Company) is very similar in structure to triseclavine. We have now concluded preliminary experiments in which men who had slept all night received one of these drugs (or placebo) at 8 a.m. Observations were made every half hour for eight hours and consisted merely of checking whether or not the men were in bed asleep, in bed awake, or up and about. This was done to avoid any stimulation which might obscure sedative or hypnotic effect. Under these conditions the men slept more after all three drugs than after placebos. Lilly 23194 was the most potent compound, 40 mcg./kg. causing an average increase (5 patients) of 1.7 hours sleep in the four hours between 8 and 12 a.m. Agroclavine (50-60 mcg./kg.) was the next most potent, causing an increase of 1.2 hours (6 patients). Dihydro-agroclavine (60-70 mcg./kg.) was least potent, causing an average

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increase of only 0.5 hours (4 patients). Onset of action was very rapid with the two active drugs, the men being unable to remain awake an half-hour after the drug was given. After 12 o'clock the men slept little, but reported subjective relaxation and drowsiness lasting through the afternoon.

These results are of interest because of the reversal of the predicted effect (excitation expected, sedation observed), the discrepancy with animal tests (drugs are LSD-like in animals), and apparent high potency as hypnotic drugs in man. You will note that the total dose of 23194 was only 2-3 mg; the implications are obvious.

We are now extending these observations. The most potent drug (Lilly, 23194) will be compared at two dose levels (2 and 4 mg. per 70 kg.) with secobarbital (100 and 200 mg.) and the dose range of agroclavine and dihydroagroclavine will be further explored. In addition, we are also adding studies on d-Lysergic acid diethylamide, which in preliminary tests also seemed to have sedative effects in doses as low as 15-20 mcg./kg. Nine men will receive these drugs so that we will have figures which will have some statistical meaning. I then plan to attempt to attenuate the LSD reaction with Lilly 23194, and may study some combinations of these drugs with alcohol and other hypnotics.

C-5. I am attaching a long overdue report on C-5. As I told you, this compound appears to be relatively inert in man.

Neurophysiological Studies on C-9. These studies are being undertaken by Dr. William R. Martin as part of a larger project.

Dr. Martin has found that, in intact cats, 0.2-0.4 mg./kg. of C-9 intravenously causes depression of body temperature, ataxia, relaxation of nictitating membrane, depression of the pinnal reflex, diminished muscle tone, loss of righting reflex, somnolence, and taming. These effects appear after two hours and may persist for as long as three days (0.4 mg./kg.). Bradycardia, which has been shown to be due to the temperature fall, is also observed. In unanesthetized curarized cats with electrodes in cortex and in the reticular formation in the mesencephalon C-9 causes marked EEG slowing; increase in the threshold for activation of the EEG; decreased lengths and altered quality of the activation response; fall in blood pressure, with narrow pulse pressure; increased threshold for elicitation of a blood pressure rise by mesencephalic stimulation; and decrease in pressure response once it has been elicited.

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During a visit to the University of Rochester I have also learned that Dr. E. S. Boyd of the Department of Pharmacology has become interested in this group of drugs. He has tested the methyl- and dimethyl-heptyl-derivatives and is attempting to study the effects in cats with the view of investigating the metabolic fate of the compounds. You are doubtless aware of his work.

K-302. A report on this material, and on the crude form, is attached. As I told you previously, both the crude material and K-302 are active.

Psilocybin. Attached is a thermofax copy of letter from Dr. Henze of Sandoz indicating that psilocybin will be available to me in the near future. I should be able to undertake preliminary work with this compound about the middle or end of November.

Narcotics of High Potency. Dr. P. Janssen of Eupharma Laboratories, Belgium, visited us this month. He told us about some benzimidazoles with analgesic properties of extreme potency. These compounds belong to the series originally developed by Ciba. One of Janssen's compounds is said to be 3-thousand times as potent as morphine in monkeys; and another, a rather unstable fluorinated compound, is 300-thousand times as potent as morphine. I believe that Dr. Janssen talked with Dr. N. B. Eddy and with persons from the Army Chemical Center concerning these drugs. It is quite likely that members of this series will come to us via the Drug Addiction Committee after testing in monkeys in Michigan has been completed.

Inventory for Subjective Effects of Drugs. My psychological staff is attempting to develop a self-administered machine-scored "inventory" which will discriminate between the subjective effects of opiates, barbiturates, alcohol, chlorpromazine, amphetamines, LSD, and pyrahexyl. In its present form the test consists of more than 500 true or false items and includes validating and lying scales. The number of items will be sharply reduced after item analysis has been done, and it may be possible to develop sub-inventories for each of these classes of drugs. We hope that the inventory will improve our methods for measuring the subjective effects of the drugs and that the inventory can eventually become a quantitative instrument. The project is however very long-range and may require as much as two more years for completion.

I expect to be in Lexington for the next three months except for November 20 and 23, when I will meet with the Council on Mental Health, AMA, in Chicago. I would welcome a visit from you at any time.

With kindest personal regards,

Sincerely yours,

Harris Isbell

Harris Isbell, M.D.
Director

Enclosures

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